REMARKS

Claims 6-8 have been amended herein. No claims have been canceled or added herein. Therefore, claims 1-8 are pending and under active consideration.

Claims 6-8 stand rejected under 35 U.S.C. 112 "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> (A) Claim 6 recites the term "n [sic]". However, the nature of the term "n [sic]" is not clear, rendering the claim vague and indefinite.
>
> (B) Claim 6 lacks antecedent basis for the term "n [sic]". (i.e. it has not been established that this term [has] the meaning indicated in claim 1).
>
> (C) Claim 7 provides for a method of using nucleoside derivatives in the manufacture [of] oligonucleotides, but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.
>
> (D) The phrase, in claim 8, line 3-4, "reagents and adjuvants as well as solvents" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicant respectfully traverses the foregoing rejection. Insofar as the foregoing rejection pertains to claim 6, Applicant has amended claim 6 so that the language in question is no longer recited; consequently, with respect to claim 6, the rejection is moot. Insofar as the foregoing rejection pertains to claim 7, Applicant has amended claim 7 so that it now positively recites certain process steps; therefore, with respect to claim 7, the rejection has been overcome. Insofar as the

foregoing rejection pertains to claim 8, Applicant has amended claim 8 so that it is clear that the reagents, adjuvants and solvents recited by the claim are those that are suitable for the automatic synthesis of oligonucleotides. Applicant respectfully submits that one of ordinary skill in the art is capable of discerning which reagents, adjuvants and solvents are suitable for the stated purpose, and examples of several suitable reagents, adjuvants and solvents are disclosed in Examples 1 and 2 of the present specification.

Accordingly, for at least the above reasons, the foregoing rejection should be withdrawn.

Claim 7 stands rejected under 35 U.S.C. 101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101."

Applicant respectfully traverses the foregoing rejection. As noted above, claim 7 has been amended in this paper. Applicant respectfully submits that claim 7, thus amended, constitutes a proper process claim.

Accordingly, for at least the above reasons, the foregoing rejection should be withdrawn.

Claims 1-8 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Holmes et al. (WO 94/10128) in view of Giegrich et al. (Nucleosides and Nucleotides, 17, 1987-1996, 1998)." In support of the rejection, the Patent Office states the following:

> The claims 1-8 are directed to 2-(O-nitrophenyl)ethoxythiocarbonyl-protected nucleoside derivatives, a method of preparation of the said derivatives using thiophosgene, the use of the said derivative in the synthesis of oligonucleotides and a kit containing the said nucleoside derivative. Additional claim limitations claimed include R_1 as adenine, cytosine, guanine, thymine or uracil, R_2-R_7 as an H atom or an alkyl residue or R_2 as a diisopropylamino-(2-cyanoetoxy)phosphinyl group of the formula IV.

Holmes et al. teach C-5'OH-2-(O-nitrophenyl)ethoxythiocarbonyl-protected nucleoside derivatives and a method of preparation of the said derivatives (see page 4, summary of the invention). In claims 30 and 37, the 2-(O-nitrophenyl)ethoxythiocarbonyl-protected nucleoside derivatives of a purine, a pyrimidine, or an analog thereof are disclosed. Holmes et al. also disclose a method of preparation of nucleoside derivatives having the 2-(O-nitrophenyl)ethoxythiocarbonyl-protecting group at C-5'-OH, the synthesis involves the steps of reacting a protected benzyl alcohol (Fig. 3) with phosgene to produce benzyloxycarbonyl derivative which is coupled with the 5' oxygen of a nucleoside (page 24, last para.). It would have been obvious to use the thiophosgene to react with the benzyl alcohol of formula II (claim 6) to prepare the thiocarbonyl chloride which is coupled with the 5' oxygen of a protected nucleoside. While the Holmes et al's 2-(O-nitrophenyl)ethoxythiocarbonyl-protected nucleoside derivatives and a process for their preparation are closely analogous to the applicant's nucleoside derivatives and the method of their production, Holmes et al's. 2-(O-nitrophenyl)ethoxythiocarbonyl-protected nucleoside derivatives differ from applicant's 2-(O-nitrophenyl)ethoxythiocarbonyl-protected nucleoside derivatives in that the C-2'-OH is not substituted with a diisopropylamino-(2-cyanoethoxy)phosphinyl group.

Giegrich et al. teach a nucleoside protected by the 2-(2-nitrophenyl)ethylsulfonyl group (see abstract). Giegrich et al. disclose the nucleoside derivatives wherein the C-5'-OH is protected by 2-(O-nitrophenyl)ethoxycarbonyl group and C-2'-OH is protected by diisopropylamino-(2-cyanoethoxy)phosphinyl group (see figures on page 1992). It is noted that von Giegrich et al. does not provide specific disclosures regarding the use of a 2-(O-nitrophenyl)ethoxythiocarbonyl protecting group at C-5'-OH.

Therefore, one of ordinary skill in the art would have found the applicants claimed C-5'-OH-2-(O-nitrophenyl)ethoxythiocarbonyl- and C-2'-OH-diisopropylamino-(2-cyanoethoxy)phosphinyl protected nucleoside derivatives, a method of their preparation to have been obvious at the time the invention was made having the above cited references before him. Since Holmes et al. teach C-5'-OH-2-(O-nitrophenyl)ethoxythiocarbonyl-protected nucleoside derivatives and a method of preparation of the said derivatives and Giegrich et al. teach a nucleoside protected at C-2'-OH by the diisopropylamino-(2-cyanoethoxy)phosphinyl group,

one skilled in the art would have a reasonable expectation for success in combining both references to accomplish a nucleoside derivative protected by the 2-(O-nitrophenyl)ethoxythiocarbonyl at C-5'-OH and diisopropylamino-(2-cyanoethoxy)phosphinyl at C-2'-OH and a process for their preparation. The motivation for doing so is provided by Holmes et al., which suggests the use of ortho-nitrobenzyl photosensitive protecting groups to protect functional groups of nucleosides from unwanted side reactions during polymer synthesis (page 4, lines 15-24).

With respect to claim 8, the Patent Office states the following:

> Regarding claim 8, the printed matter on a label or package insert (operating instructions) does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture. See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned. In accordance with the patent statutes, an article or composition of matter, in order to [be] patentable, must not only be useful and involve invention, but must also be *new*. If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in an of itself, new.
>
> Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak 217 USPQ 401 (CAFC) relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed articles. The

nucleoside derivatives of Holmes et al. remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Thus the instructions for use included a kit or article manufacture constitute an "intended use" for that kit or article or manufacture. Intended use does not impart patentable weight to a product. See MPEP 2111.03: Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey, 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963).

In the instant case, the claims are drawn to an article of manufacture which comprises oligonucleotides, and operating instructions. The intended synthesis which is recited on the label or package insert lacks a function relationship to the nucleoside derivative because the insert or label does not physically or chemically affect the chemical nature of the nucleoside derivative within the article of manufacture. Therefore the synthesis of oligonucleotides which is comprises within the article of manufacture is unpatentable over the prior art nucleoside derivative, because they function equally effectively with or without the labelling, and accordingly *no functional relationship exists between the instructions for synthesis and the nucleoside derivative.* (Emphasis in original.)

Applicant respectfully traverses the foregoing rejection. The present application relates to 2-(*o*-nitrophenyl) ethoxy**thio**carbonyl-protected nucleoside derivatives (claims 1-5), a method for preparing such derivatives (claim 6), a method of using such derivatives (claim 7), and a kit including the derivatives (claim 8).

Holmes et al., contrary to the assertion of the Patent Office, does not relate to 2-(*o*-nitrophenyl) ethoxythiocarbonyl-protected nucleosides derivatives. Instead, Holmes et al. discloses nucleosides protected by 2-(*o*-nitrophenyl) methoxy or 2-(*o*-nitrophenyl) methoxythiocarbonyl groups. The mechanism for the photoremoval of the Holmes 2-(*o*-nitrophenyl) methoxythiocarbonyl group is markedly different than the mechanism for the photoremoval of the claimed 2-(*o*-nitrophenyl) ethoxythiocarbonyl group, based in part on the presence in the claimed derivatives of an additional carbon atom in the chain which is to be protected. Therefore, one of ordinary skill in the art would not have been motivated to modify Holmes et al. to arrive at the claimed invention.

Giegrich et al., which relates to nucleosides protected by 2-(*o*-nitrophenyl) ethoxycarbonyl groups, differs from the claimed 2-(*o*-nitrophenyl) ethoxy**thio**carbonyl-protected nucleoside derivatives in that Giegrich lacks the sulphur atom present in the claimed derivatives. Because a sulphur atom is larger and less electronegative than an oxygen atom and because the Π-C=S bonds (2p-3p) are not as stable as the C=O bonds (2p-3p), the reactivity of the claimed 2-(*o*-nitrophenyl) ethoxythiocarbonyl group is not the same as that of the Giegrich ethoxycarbonyl group. In fact, Applicant has found that the decomposition of the claimed thiocarbonyl compounds is significantly faster and to a much higher percentage than is the decomposition of the Giegrich carbonyl compounds. Such results are neither taught nor suggested by the references. In fact, one of ordinary skill in the art would not have had a reasonable expectation that the claimed 2-(*o*-nitrophenyl) ethoxythiocarbonyl groups would be successful as photolabile protecting groups for nucleosides.

Accordingly, for at least the above reasons, the foregoing rejection should be withdrawn.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

By: _____

Edward M. Kriegsman
Reg. No. 33,529
665 Franklin Street
Framingham, MA 01702
(508) 879-3500

Dated: March 24, 2004

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on March 24, 2004

_____

Edward M. Kriegsman
Reg. No. 33,529
Dated: March 24, 2004